Summary for Presentation to FDA Advisory Committee (VRBPAC)

Otitis Media Indication

Pneumococcal 7-valent Conjugate Vaccine
(Diphtheria CRM_{197} Protein)
PREVNAR®

Wyeth Vaccines Research
April 22, 2002

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Abbreviations

AOM	acute otitis media
DTaP	Diphtheria, tetanus, acellular pertussis vaccine
EAC	External Advisory Committee
FinOM	Finnish Otitis Media Vaccine Study
HbOC	Haemophilus b oligosaccharide conjugate vaccine
HBV	Hepatitis B Vaccine
IPV	Inactivated Poliovirus Vaccine
ITT	intent-to-treat
MEF	middle ear fluid
MMR	Measles, Mumps, Rubella Vaccine
MSD	Merck, Sharpe, and Dohme
MnCC	Meningococcal C Conjugate Vaccine, Meningitec®
NCKP	Northern California Kaiser Permanente
OPV	Oral Poliovirus Vaccine
PCR	polymerase chain reaction
PP	per-protocol
SAE	serious adverse event

1.0 Introduction

1.1 Background

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), Prevnar®, is a sterile, liquid preparation which contains saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, individually conjugated to diphtheria CRM_{197} protein. The vaccine was licensed by the Food and Drug Administration in the US on February 17, 2000 for use against invasive pneumococcal disease caused by the seven pneumococcal serotypes included in the vaccine. As of March 2002, there have been approximately 26.2 million doses of Prevnar distributed in the US since licensure. The routine use of this vaccine is substantially reducing the incidence rates of invasive pneumococcal disease in the US.[1, 2]

At this time, Wyeth Vaccines is pursuing the addition of an otitis media indication to the license for Prevnar. This briefing document provides a summary of the clinical data supporting the use of Prevnar for prevention of otitis media. Details of the statistical hypothesis testing structure, analysis methods, and significance levels of the AOM outcomes of each study are provided in Appendix 1. Additional safety information, including an overview of safety in the FinOM Efficacy Study and a list of changes and proposed changes to the safety section of the product labeling, are included in Appendix 2.

1.2 Epidemiology of Pneumococcal Otitis Media

Acute otitis media (AOM) is an extremely common childhood disease. In the US, 24.5 million ambulatory care visits and 490,000 procedures for myringotomy with tube placement are attributed to otitis media annually.[3, 4] Complications of AOM include persistent middle ear effusion, chronic otitis media, transient hearing loss and speech delays, and if left untreated, may lead to more serious diseases, such as mastoiditis and meningitis.

The peak incidence of AOM is 6 to 18 months of age,[5] but in a 1990 survey by the Centers for Disease Control and Prevention (CDC), otitis media was the most common principal illness diagnosis in children 2-10 years of age.[6] Moreover, according to one study in the greater Boston area,[5] most children have multiple episodes of AOM. Thus, by 1 year of age, 62.4% of children had experienced at least one episode of AOM, 17.3% at least 3 episodes, and 1% at least 6 episodes. By the end of the third year of life, 83.9% of children had at least 1 episode of AOM, 46.2% at least 3 episodes, and 16.3% had at least 6 episodes,[5] and by age 7, the corresponding

figures are 93.4% (≥ 1 episode), 73.9% (≥ 3 episodes), and 39.2% (≥6 episodes). A variety of host and environmental risk factors appear to underlie a tendency for multiple episodes, including the finding that the onset of otitis media in the first several months of life is highly associated with subsequent recurrent disease.[7]

Streptococcus pneumoniae is the bacterial pathogen most commonly isolated from middle ear fluid, identified in 20 to 40% of middle ear fluid cultures in AOM.[8, 9] Pneumococcal otitis media is associated with higher rates of fever and is less likely to resolve spontaneously (19%) than AOM due to either nontypeable *H. influenzae* (48%) or *M. catarrhalis* (75%).[10, 11] Although more than 90 immunologically distinct pneumococcal serotypes have been reported, recent metanalyses of 21 data sets from several countries[12, 13] suggest that the most common 8-9 serotypes account for at least 75% of all observations in children ≥6 months of age, and at least 60% of observations in children 0-5 months old. The major serotypes identified in almost all data sets include, in descending order of prevalence, 19F, 23F, 14, 6B, 6A, 19A, and 9V. In addition, these serotypes constitute a higher proportion of pneumococcal isolates in children 6-18 months of age, the age range of highest AOM incidence, than in the younger (<6 months) or older age groups (>18 months).[13]

In the US, there are 7 data sets of middle ear fluid isolates for which pneumococcal serotype- and/or serogroup-specific information are available, and the results are remarkably consistent. In a review, published in 1981, of 1837 children with AOM,[14] Klein et al indicated that the 7 serogroups represented in Prevnar (4, 6, 9, 14, 18, 19, and 23) accounted for 69.9% of all pneumococcal middle ear fluid isolates. A second study conducted from 1985 to 1989 with 228 children indicated a Prevnar serogroup-specific coverage of 79.6%.[15] Two studies published in 1995[16, 17] and comprising a total of 470 isolates reported that approximately 70% of AOM isolates due to *S. pneumoniae* belonged to serogroups represented in Prevnar. Three recent data sets that contain 1200 middle ear fluid isolates collected since 1994 each reported that serogroups represented in Prevnar comprised 82-86% of all AOM pneumococcal MEF isolates.[13,18,19] These figures include vaccine-related serotypes (e.g. 19A, 6A) which accounted for 13.9 to 17.1% of the pneumococcal isolates. Finally, in a study of 28 US children with pneumococcal mastoiditis, a severe complication of acute or chronic otitis media, serogroups 19, 23, 9, and 14 together accounted for 85% of cases of mastoiditis.[20]

Over the past decade, the prevalence of drug-resistant pneumococci has rapidly increased in the US and several other countries[21] complicating therapy of pneumococcal AOM.[17, 22] Conversely, as noted by Giebink,[21] since antibiotics are prescribed empirically to virtually all children with

AOM in the US, the treatment of this condition in itself is a major contributor to the rise of drug-resistant pneumococci. By one report, nearly one-half of antibiotics prescribed for children younger than 10 years of age in 1986 was for otitis media.[23]

In a multivariate analysis of 9 data sets from 3232 children with pneumococcal AOM that controlled for a variety of potentially confounding variables, including age and geographic location, serotypes in Prevnar were found to be far more likely to be resistant to penicillin than were other serotypes.[13] Specifically, Prevnar serotypes 6B, 9V, 14, 19F, and 23F, and related serotypes 6A and 19A account for the vast majority of penicillin and multi-drug resistance both in the US and elsewhere[19,22] As a consequence, in an analysis of 500 US pneumococcal otitis media isolates,[19] Prevnar serotypes comprised 78.3% of the 286 penicillin non-susceptible isolates, and vaccine-related serotypes comprised virtually all the remainder (19.9%). In that study, each of the 161 isolates that showed multiple-drug resistance was either a vaccine or vaccine-related serotype. Similar results have been reported from other countries.[22, 24]

1.3 Rationale for the Addition of the Otitis Media Indication

The effect of Prevnar immunization on otitis media has been extensively studied in approximately 40,000 children in two very different geographical settings, and reproducible decreases in otitis media episodes and in ear tube placement were determined with statistical significance. Given the large numbers of otitis media cases occurring annually in U.S. children, the decrease seen in the clinical trial setting may translate into a very large public health impact. As the Prevnar label is a controllable mechanism for providing complete and accurate data to physicians, the addition of the otitis media indication and relevant otitis media data into the Clinical Pharmacology section would allow physicians to provide parents with a more complete picture of what is known about the potential impact of Prevnar on otitis media, in addition to invasive disease. This information will balance and put into context the important contributions of Prevnar, such as reducing the number of AOM episodes, cases of recurrent AOM, and ear tube placement surgeries, with appropriate information on the epidemiology of *S.pneumoniae* as only one of many etiologic agents that cause AOM in children.

1.4 Overview of the Clinical Studies Supporting the Otitis Media Indication

Three clinical studies have been performed to assess the impact of Prevnar on otitis media. Two of the studies (D118-P809 [FinOM][25] and the Follow-up Study) were performed by the National Public Health Institute in Finland, and the other study (D118-P8) was performed by Northern California Kaiser Permanente (NCKP)[26]. The NCKP study is the same study that provided the

invasive disease efficacy data in support of the original indication for invasive pneumococcal disease. Table 1 presents an overview of some of the key elements of these studies. Further details of the study designs, definitions used, outcome variables assessed and results of each individual study can be found in the sections that follow.

Table 1: Overview of Studies Supporting the Otitis Media Indication

Study	Principal Investigators	Population	Number of Children Enrolled	Vaccine Schedule	Control	Blinding	AOM Ascertainment
D118-P809 FinOM Efficacy	Juhani Eskola, MD Terhi Kilpi, MD	Finnish Infants	1,662	2, 4, 6, 12-15 months	Hep B Vaccine	Double-Blind	Clinic Visits, Myringotomy, cultures performed
FinOM Follow-Up	Terhi Kilpi, MD	Finnish Infants	756[a]	As above	Hep B Vaccine	Unblinded	Hospital record search
D118-P8 NCKP	Steven Black, MD Henry Shinefield, MD	US Infants	34,146[b]	2, 4, 6, 12-15 months	MnCC Vaccine	Double-Blind	Automated database search for OM visits

a: These children were also part of the original D118-P809 study.
b: as of April 30, 1998, when database for otitis media data was closed.

2.0 Finnish Studies

2.1 Finnish Otitis Media Efficacy Study (FinOM), D118-P809

2.1.1 Description of Study Design, Definitions, and Outcome Variables

The D118-P809 (FinOM) study was performed by the National Public Health Institute in Finland beginning in December 1995. Eight clinics in five different centers were established in one area of Finland for this study. The primary purpose of this study was to determine the protective efficacy of two heptavalent pneumococcal conjugate vaccines (Prevnar from Wyeth Vaccines and PncOMPC from MSD) against culture-confirmed pneumococcal acute otitis media due to vaccine serotypes, compared to a control vaccine, hepatitis B vaccine (HBV). Infants were immunized at 2, 4, 6, and 12 months of age with either Prevnar, PncOPMC or hepatitis B vaccine. They also received a DTP-Hib (PRP-T or HbOC) vaccine at 2, 4, 6, and 24 months of age, IPV at 7, 12, and 24 months of age, and MMR at 18 months of age. Only the data from the Prevnar and control (HBV) groups will be presented in this document.

Follow-up for acute otitis media (AOM) was carried out in study clinics by the study personnel who were responsible for the routine visits. Parents of study participants were encouraged to bring their child to the study clinics if the child had respiratory symptoms suggesting acute otitis media. Myringotomy with aspiration was done if AOM was diagnosed at the visit. Bacterial culture of the middle ear fluid (MEF) was performed, and if pneumococcus was found, serotyping was also done.

Key definitions that were employed in this study are presented in Table 2.

Table 2: Definitions of AOM Episodes

	Definition
Acute Otitis Media (AOM)	A visually abnormal tympanic membrane (in regard of color, position and/or mobility) suggesting effusion in the middle ear cavity, concomitantly with at least one of the following signs and/or symptoms of acute infection: fever, ear ache, irritability, diarrhea, vomiting, acute otorrhea not caused by external otitis, or other symptoms of respiratory infection
AOM Episode Due to Vaccine Serotypes	Culture-confirmed pneumococcal AOM due to any of the seven serotypes included in the study vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). A new episode was considered to start if at least 30 days had elapsed since the beginning of the last AOM episode due to the same serotype or any interval for different vaccine serotypes.
Culture-Confirmed Pneumococcal AOM Episode	Culture-confirmed AOM due to *Streptococcus pneumoniae* of any serotype(s). A new episode started if at least 30 days had elapsed since the beginning of the last culture-confirmed pneumococcal AOM episode, irrespective of serotype.
Pneumococcal AOM Episode by Culture or PCR	AOM in which *Streptococcus pneumoniae* is detected in the middle ear fluid (MEF) either by culture or pneumococcal pneumolysin polymerase chain reaction (PCR). A new episode started if at least 30 days had elapsed since the beginning of the last pneumococcal AOM episode.
AOM Episode with MEF	AOM in which at least one ear was indicated for MEF sample and the sample was obtained. A new episode starts if at least 30 days had elapsed since the beginning of the last AOM episode with MEF sample regardless the findings in MEF.

Table 2: Definitions of AOM Episodes

	Definition
AOM Episode Regardless of Etiology	A clinical AOM diagnosis regardless of etiology. A new episode started if at least 30 days had elapsed since the beginning of the last AOM episode.
AOM Episode Due to Vaccine-Related Serotypes	Culture-confirmed pneumococcal AOM due to any of the five serotypes related to vaccine serotypes (6A, 9N, 18B, 19A, and 23A). A new episode was considered to start if at least 30 days had elapsed since the beginning of the last AOM episode due to the same serotype or any interval for different vaccine serotypes.
AOM Episode Due to Other Serotypes	Culture-confirmed pneumococcal AOM due to any serotype other than the seven vaccine serotypes and the five vaccine-related serotypes (4, 6A, 6B, 9V, 9N, 14, 18C, 18B, 19F, 19A, 23F and 23A). A new episode was considered to start if at least 30 days had elapsed since the beginning of the last AOM episode due to the same serotype or any interval for different vaccine serotypes.
AOM Episode Due to an Individual Serotype	Culture-confirmed pneumococcal AOM due to a given serotype. A new episode was considered to start if at least 30 days had elapsed since the beginning of the last AOM episode due to the same serotype.
Recurrent AOM	A child was considered to have recurrent AOM if the child experienced ≥ 3 AOM episodes (regardless etiology) in 6 months or ≥ 4 episodes in 12 months at any time during follow-up.

Definition of Analyses Populations and Follow-up

- **Per-Protocol Follow-Up (PP)**

A child was considered vaccinated per-protocol if the following criteria were met:

- first dose was administered at 6 – 13 weeks of age, second dose was administered at 14-21 weeks of age, third dose was administered at 22-29 weeks of age, and fourth dose was administered at 11-14 months of age.

- interval between primary series doses was 42-83 days

The per-protocol follow-up period started 14 days after the third dose and continued until the day of discontinuation as per protocol or on the day of the close-out visit at the age of 24 months. If there was no discontinuation as per protocol and the close-out visit was delayed beyond the per-

protocol period (24 months + 4 weeks), the per-protocol follow-up period ended on the child's second birthday. The reasons for discontinuation from per protocol follow-up were:

1) death of the child
2) withdrawal of consent to participate in study
3) relocation of family out of area and inability to attend study clinics
4) lost to follow-up or unable to contact
5) investigator considered that continuation in study may cause health problem to child
6) child was vaccinated with pneumococcal polysaccharide vaccine or hepatitis B vaccine
7) study code of an individual child was broken and nature of vaccine disclosed to anyone except members of the EAC
8) violation of vaccination schedule or of randomization
9) child's follow-up at study clinic was discontinued for some other reason

- **Intent-to-treat Follow-up (ITT)**

All children who were enrolled, randomized, and received a dose of study vaccine were included in the intent-to-treat population. The intent-to-treat follow-up period began on the day that the first dose was administered and continued until the date of permanent discontinuation or until the day of the closeout visit at 24 months of age. Permanent discontinuation occurred if the subject died, the parents withdrew their consent, the family moved out of the area, or the family could not be contacted. If there was no permanent discontinuation and the closeout visit was delayed beyond the per-protocol period (24 months + 4 weeks), the intent-to-treat follow-up period ended on the child's second birthday.

The outcome variables assessed in this study are described below.

Analyses Included in the Submission

Primary Efficacy Analysis:

The primary objective was to compare the risk of all AOM episodes due to vaccine serotypes between the treatment groups during per-protocol follow-up (PP). The analysis plan, explicitly outlined prior to unblinding, was to perform the primary efficacy analysis first and to proceed to other analyses to further understand the vaccine effect only if the primary analysis showed statistically significant effect (at $p < 0.05$) on the reduction of risk of all AOM episodes due to vaccine serotypes.

An analysis of all AOM episodes due to vaccine serotypes during the intent-to-treat (ITT) follow-up was also performed.

Other Efficacy Analyses and Endpoints (PP and ITT):

- First AOM episode due to vaccine serotype
- Subsequent vaccine serotype episodes
- Vaccine serotype episodes by dose
- Culture-confirmed pneumococcal AOM episodes regardless of serotype
- Pneumococcal AOM episodes as determined by either culture or PCR
- AOM episodes with MEF regardless of etiology
- AOM episodes regardless of etiology
- Recurrent AOM

Post-Hoc Analyses

- AOM episodes due to vaccine-related serotypes
- AOM episodes due to serotypes unrelated to vaccine serotypes
- AOM episodes due to individual serotypes in the vaccine serogroups

Post Submission Analyses

- Covariate Analysis
- Sensitivity Analysis Using Alternative Definition of Episode
- Tympanostomy Tube Placement

2.1.2 Results of AOM Outcomes

A total of 1662 infants were equally randomized to receive either Prevnar or control (HBV) vaccine (831 subjects in each group). Of these, 811 subjects in the Prevnar group and 821 in the control group completed the primary series vaccination per protocol and started the per-protocol follow-up. Among them, 786 subjects (94.6%) in the Prevnar group and 794 (95.5%) in the control group completed the per-protocol follow-up at 24 months of age.

Table 3 presents the demographic characteristics of the randomized population at baseline and during the trial, including gender, AOM history prior to enrollment, gestational age, birth weight, daycare attendance, breast-feeding, and household smoking status. The two groups were similar with respect to gender, breast-feeding history, and household smoking history. There were slightly more subjects in the HBV group with an AOM history prior to enrollment, with a

gestational age less than 37 weeks, or with birth weight less than 2.5 kg (a difference between groups of 1.2%, 1.5%, and 2.1%, respectively). There were, on the other hand, more subjects in the Prevnar group attending daycare at 12 and 18 months of age (a difference between groups of 3.5% and 5.1%, respectively).

Table 3: Baseline Characteristics and Potential Risk Factors of Intent-to-Treat Population

		% Subjects (Number of Subjects)		
		HBV	**Prevnar**	**P-value[a]**
Number Randomized		831	831	
Gender	Male	51.5 (428)	52.3 (435)	0.768
AOM Prior to Enrollment	Yes	4.7 (39)	3.2 (27)	0.166
Gestational Age	< 37 weeks	6.4 (53)	4.9 (41)	0.243
Birth Weight	< 2.5 kg	5.1 (42)	3.0 (25)	0.045
Daycare Attendance[b]	6 months of age	1.0 (8)	1.0 (8)	>0.999
	12 months of age	13.8 (115)	17.3 (144)	0.058
	18 months of age	29.7 (247)	34.8 (289)	0.031
Breast-feeding	< 6 months	45.2 (376)	44.5 (370)	0.805
Household Smoking	Reported at ≥ 1 visits	35.0 (291)	36.7 (305)	0.506

a: Based on Fisher's exact test.
b: This includes attending family day care and day care center. Subjects with unknown daycare status (total of 0.8%, 1.9%, and 2.8% of subjects at 6 months, 12 months, and 18 months of age, respectively) were also included.

Analyses Included in the Submission

Primary Efficacy Variable

The point estimate for efficacy of Prevnar against culture-confirmed vaccine-serotype AOM in the PP analysis was 57%, with the 95% confidence interval from 44% to 67%, as presented in

Table 4. A similar vaccine efficacy, 54% (95% CI: 41, 64), was seen in the ITT analysis, with follow-up starting after the first dose at 2 months of age.

Table 4: Summary Of Results of Primary Analysis in the FinOM Study

		Number of Episodes		Rate/person year		Vaccine Efficacy (%)	
Type of Episode	**Follow-up Period**	**HBV**	**Prevnar**	**HBV**	**Prevnar**	**Estimate**	**95%CI**
AOM due to vaccine serotypes	PP	250	107	0.21	0.09	57	(44, 67)
	ITT	292	135	0.20	0.09	54	(41, 64)

Other Efficacy Variables

Table 5 presents the results of additional efficacy analyses. These include the efficacy against the first and subsequent AOM episodes, culture-confirmed pneumococcal AOM episodes, pneumococcal AOM episodes by culture or PCR, AOM episodes with MEF, AOM episodes regardless of etiology, and recurrent AOM. The results in both the per-protocol and intent-to-treat populations are presented.

Vaccine efficacy against the first episode of vaccine–serotype AOM was 52% (95% CI: 39, 63) and for subsequent episodes in children who already had a first episode was 45% (95% CI: 5, 69). The compounded effect on the first episode and subsequent episodes yielded an overall efficacy against vaccine-serotype AOM of 57%, as presented above in Table 4. For all culture-confirmed pneumococcal AOM, the efficacy was 34% (95% CI: 21, 45). In addition to the gold standard of culturing, PCR was also used to detect pneumococcus in this trial. When the pneumococcus was identified by PCR or by culturing, the efficacy estimate was 20% (95% CI: 7, 31). (Further discussions of the outcomes using PCR are included in Appendix 3).

The overall vaccine efficacy against all AOM episodes, regardless of etiology, was 6% (95% CI: -4, 16). As the vaccine is not expected to prevent AOM due to other pathogens, it is not surprising to see that the overall efficacy was substantially lower than the efficacy against pneumococcal AOM. Vaccine efficacy against recurrent AOM was 16% (95% CI:-6, 35).

Table 6 presents the efficacy results by dose. The efficacy against vaccine-serotype episodes increased with the first three doses: 21% (95% CI: -75, 65) during the period between doses 1 and 2, 43% (95% CI: -10, 71) between doses 2 and 3, and 57% (95% CI: 36, 72) between doses 3 and 4 in the PP population. The confidence intervals for the efficacy estimates between doses 1 and 2 and between doses 2 and 3 were wide due to the short follow-up time and limited number of episodes.

Table 5: Summary Of Efficacy Results For Additional Analyses

Outcome Measure	Follow-up Period	Number of Episodes		Rate/person year		Vaccine Efficacy (%)	
		HBV	Prevnar	HBV	Prevnar	Estimate	95%CI
First AOM Episode due to Vaccine Serotype	PP	177	89	0.171	0.081	52	(39, 63)
	ITT	196	109	0.152	0.079	48	(34, 59)
Subsequent AOM Episode (after first VT episode) due to Vaccine Serotype	PP	73	18	0.467	0.249	45	(5, 69)
	ITT	96	26	0.491	0.250	49	(20, 67)
All culture-confirmed pneumococcal AOM episodes	PP	414	271	0.36	0.23	34	(21, 45)
	ITT	467	322	0.32	0.22	32	(19, 42)
All pneumococcal AOM episodes by culture or PCR[a]	PP	678	548	0.60	0.48	20	(7, 31)
	ITT	764	635	0.54	0.44	18	(5, 29)
AOM episodes with MEF	PP	1267	1177	1.16	1.09	7	(-5, 17)
	ITT	1445	1390	1.06	1.01	4	(-7, 14)
AOM episodes regardless of etiology	PP	1345	1251	1.24	1.16	6	(-4, 16)
	ITT	1532	1474	1.13	1.08	4	(-7, 14)
Children with recurrent AOM episodes	PP	149	123	0.125	0.104	16	(-6, 35)
	ITT	174	158	0.117	0.106	9	(-12, 27)

a: Additional details on the analysis of data for PCR or culture-confirmed pneumococcal AOM can be found in Appendix 3.

Table 6: Summary Of Efficacy Results By Dose

Type of Episode	Follow-up Period	Population[a]	Number of Episodes		Rate/100 person year		Vaccine Efficacy (%)	
			HBV	Prevnar	HBV	Prevnar	Estimate	95%CI
AOM due to vaccine serotypes by dose								
Dose 1	2 to 4 months of age	PP	14	11	0.11	0.09	21	(-75, 65)
		ITT	14	11	0.11	0.09	22	(-74, 65)
Dose 2	4 to 6 months of age	PP	23	13	0.18	0.10	43	(-10, 71)
		ITT	24	13	0.19	0.10	46	(-4, 72)
Dose 3	6 to 12 months of age	PP	92	39	0.24	0.10	57	(36, 72)
		ITT	93	40	0.24	0.10	57	(36, 71)
Dose 4	12 to 24 months of age	PP	158	68	0.20	0.09	56	(41, 68)
		ITT	159	71	0.20	0.09	55	(39, 67)

a: These are the populations that eventually qualify as per-protocol or intent-to-treat.

Post-Hoc Analyses

Because of the highly significant vaccine effect, further analyses were performed to understand the vaccine's effect in greater depth. These analyses included efficacy against individual vaccine serotypes, vaccine-related serotypes, and unrelated serotypes.

The efficacy results against individual vaccine serotypes and vaccine-related serotypes are presented in Table 7. Among the seven serotypes contained in the vaccine, the highest efficacy of 84% (95% CI: 62, 93), was seen for serotype 6B. Similar efficacy estimates were seen for serotypes 14, 23F, 18C, 9V, and 4 at 69%, 59%, 58%, 54%, and 49% respectively. The width of the confidence intervals and the significance level, however, varied depending on the prevalence of the specific serotype. The efficacy estimate for serotype 19F episodes was substantially lower than the other serotypes at 25% (95% CI: -14, 51). A significant reduction of AOM episodes due to serotype 6A, a serotype not contained in the vaccine but closely related to vaccine type 6B, was also seen with a vaccine estimate of 57% (95% CI: 24, 76).

As shown in Table 8, with all related serotypes (6A, 9N, 18B, 19A, 23A) combined, the efficacy of the vaccine was 51% (95% CI: 27, 67). The combined efficacy of the vaccine against AOM episodes caused by unrelated serotypes was -34% ($p=0.060$ for PP analysis, Table A.1 in Appendix 1). However, the net effect of Prevnar across all pneumococcal serotypes, as previously mentioned, was a significant reduction in all culture-confirmed pneumococcal AOM episodes ($p<0.0001$, Table A.1 in Appendix 1) with a vaccine efficacy estimate of 34% (95% CI: 21, 45).

For all of the endpoints discussed above, the ITT analyses showed similar results and led to similar conclusions.

Table 7: Summary of Efficacy Results of Individual Serotypes

AOM Episode due to Serotype	Follow-up Period	Number of Episodes		Rate/100 person year		Vaccine Efficacy (%)	
		HBV	Prevnar	HBV	Prevnar	Estimate	95%CI
Vaccine Serotypes							
4	PP	4	2	0.34	0.17	49	(-176, 91)
	ITT	4	2	0.27	0.13	50	(-172, 91)
6B	PP	56	9	4.71	0.76	84	(62, 93)
	ITT	61	12	4.12	0.81	80	(60, 90)
9V	PP	11	5	0.92	0.42	54	(-48, 86)
	ITT	11	6	0.74	0.40	45	(-66, 82)
14	PP	26	8	2.18	0.68	69	(20, 88)
	ITT	31	8	2.09	0.54	74	(34, 90)
18C	PP	17	7	1.43	0.59	58	(-4, 83)
	ITT	18	7	1.21	0.47	61	(2, 85)
19F	PP	58	43	4.88	3.66	25	(-14, 51)
	ITT	67	60	4.53	4.06	10	(-32, 39)
23F	PP	82	33	6.91	2.81	59	(35, 75)
	ITT	104	40	7.04	2.70	62	(41, 75)
Vaccine-Related Serotypes							
6A	PP	45	19	3.78	1.61	57	(24, 76)
	ITT	48	23	3.24	1.55	52	(17, 72)
9N	PP	8	2	0.67	0.17	75	(-24, 95)
	ITT	9	2	0.61	0.13	78	(-6, 95)
18B	PP	1	2	0.08	0.17	-103	(-2130, 82)
	ITT	1	2	0.07	0.13	-101	(-2108, 82)
19A	PP	26	17	2.18	1.44	34	(-26, 65)
	ITT	28	22	1.89	1.48	21	(-40, 56)
23A	PP	4	1	0.34	0.08	75	(-151, 97)
	ITT	4	1	0.27	0.07	75	(-149, 97)

Table 8: Rates of AOM episodes due to vaccine serotypes, vaccine related and other serotypes

Type of episode (per protocol follow-up)	Episodes		Rate/100 person year		Vaccine Efficacy (%)	
	HBV	Prevnar	HBV	Prevnar	Estimate	95%CI
AOM due to vaccine serotypes						
PP	250	107	21	9	57	44, 67
ITT	292	135	20	9	54	41, 64
AOM due to vaccine related serotypes						
PP	84	41	7.0	3.5	51	27, 67
ITT	90	50	6.1	3.4	44	20, 62
AOM due to other than vaccine related serotypes						
PP	95	126	8.0	10.7	-34	-81, 0
ITT	101	140	6.8	9.4	-39	-86, -3
All culture-confirmed pneumococcal AOM						
PP	414	271	36	23	34	21, 45
ITT	467	322	32	22	32	19, 42

Post Submission Analyses

The following post-submission analyses were performed per CBER's request to explore the potential influence of demographic or risk factors on vaccine efficacy and to explore the robustness of the efficacy conclusions with respect to the definition of vaccine-serotype episodes. In addition, the frequency of tympanostomy tube placement procedures during the FinOM efficacy trial period was also determined, although it was not an original efficacy endpoint.

Covariate Analysis

To determine whether the vaccine efficacy estimates were robust against a potentially imperfect distribution of risk factors between the two treatment groups, analyses that incorporated AOM history prior to enrollment and other potential risk factors (gender, gestational age, birth weight, daycare attendance, breastfeeding, and household smoking) as covariates were performed. The

significance levels of the main effect of each of the covariates and its interaction with vaccine effect were evaluated and are presented in Table 9. The effect of gender, AOM history prior to enrollment, and daycare attendance on the number of AOM episodes were highly significant as indicated by the p-values of the main effect. However, the interaction between these variables and the vaccine effect was not significant at the 0.05 level. Thus, in spite of the significant impact of these factors on the overall incidence of episodes, there was no evidence to suggest significantly different vaccine effect in different populations defined by these factors. Similarly, no significant interactions were seen at the 0.05 level between vaccine effect and gestational age, birth weight, breastfeeding, or household smoking. Vaccine efficacy estimates with adjustments made for these covariates were similar to the unadjusted estimates in the original analyses as shown in Table 10.

Table 9: Significance Levels (P-Values) of the Main Effect of Covariates and the Interactions with Vaccine in Andersen-Gill Models

	P-Values of Main Effect and Interaction with Vaccine													
	Gender		AOM Prior to Enrollment		Gestational Age		Birth Weight		Daycare Attendance		Breastfeeding		Household Smoking	
	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]
AOM due to Vaccine Serotypes														
PP	0.03	0.56	< 0.01	0.69	0.59	0.95	0.17	0.07	< 0.01	0.46	0.11	0.09	0.56	0.11
ITT	0.01	0.21	< 0.01	0.84	0.96	0.56	0.09	0.06	< 0.01	0.37	0.33	0.64	0.86	0.17
Culture-confirmed Pneumococcal AOM														
PP	0.08	0.95	< 0.01	0.89	0.77	0.75	0.09	0.26	< 0.01	0.32	0.31	0.25	0.14	0.21
ITT	0.05	0.81	< 0.01	0.81	0.45	0.28	0.04	0.12	< 0.01	0.23	0.76	0.89	0.24	0.26
AOM with MEF														
PP	< 0.01	0.83	< 0.01	0.34	0.46	0.95	0.04	0.74	< 0.01	0.83	0.93	0.80	0.22	0.16
ITT	< 0.01	0.96	< 0.01	0.39	0.45	0.70	0.04	0.46	< 0.01	0.85	0.20	0.28	0.16	0.07
AOM Regardless of Etiology														
PP	< 0.01	0.72	< 0.01	0.14	0.36	0.81	0.04	0.67	< 0.01	0.99	0.81	0.98	0.21	0.13
ITT	< 0.01	0.98	< 0.01	0.19	0.35	0.46	0.04	0.39	< 0.01	0.98	0.19	0.32	0.18	0.07

a: Main = main effect; Int. = interaction with vaccine. Due to the total number of parameters and the sparse data in the subgroups defined by low birth weigh, short gestational age, and daycare before 6 months of age, an analysis of covariance model contains all the covariates and interactions presents computational difficulty. The analysis was performed with one covariate at a time.

Values for each variable:
Daycare: 0 = no daycare / 1 = any type of daycare
Gestational age: 0 = greater than or equal to 37 weeks / 1 = less than 37 weeks
Birth weight: 0 = greater than or equal to 2.5 kg / 1 = less than 2.5 kg
Previous AOM: 0 = no previous AOM / 1 = previous AOM
Gender: 0 = female / 1 = male
Breastfeeding: 0 = no breastfeeding / 1 = breastfeeding
Smoking: 0 = no smoking / 1 = any smoking

Table 10: Vaccine Efficacy Estimates Adjusted for Gender, AOM Prior to Enrollment, Gestational Age, Birth Weight, Daycare Attendance, Breast-feeding, and Household Smoking

	Vaccine Efficacy (95% CI)	
	Un-adjusted for Covariates	**Adjusted for Covariates (Covariates Included as Main Effects in Andersen-Gill Analysis)**
AOM due to Vaccine Serotypes		
PP	57 (44, 67)	57 (45, 67)
ITT	54 (41, 64)	54 (41, 64)
Culture-confirmed Pneumococcal AOM		
PP	34 (21, 45)	36 (23, 46)
ITT	32 (19, 42)	32 (20, 43)
AOM with MEF		
PP	7 (-5, 17)	8 (-2, 18)
ITT	4 (-7, 14)	5 (-6, 14)
AOM Regardless of Etiology		
PP	6 (-4, 16)	8 (-2, 18)
ITT	4 (-7, 14)	5 (-6, 14)

Sensitivity Analysis Using an Alternative Definition of an Episode

The primary efficacy endpoint of vaccine serotype AOM episodes was re-analyzed with repeated episodes of a given serotype within a child being counted only once for the entire follow-up time regardless of the length of the interval between these episodes. As seen in Table 11, the vaccine efficacy estimates, for both the PP and ITT follow-up, were similar to that based on the original definition. Similar conclusions were also seen for the all culture-confirmed pneumococcal AOM analysis using this alternative definition.

Table 11: Summary of Efficacy Results with Subsequent AOM Episodes due to Same Serotypes Excluded

Type of Episode	Follow-up Period	Inclusion/Exclusion of Multiple Episodes of Same Serotype	Number of Episodes		Rate/person year		Vaccine Efficacy (%)	
			HBV	Prevnar	HBV	Prevnar	Estimate	95%CI
AOM due to vaccine serotypes	PP	Per Analysis Plan	250	107	0.21	0.09	57	(44, 67)
		Exclude all subsequent episodes of same serotype	216	95	0.18	0.08	55	(43, 65)
	ITT	Per Analysis Plan	292	135	0.20	0.09	54	(41, 64)
		Exclude all subsequent episodes of same serotype	239	118	0.16	0.08	51	(38, 61)
All culture-confirmed pneumococcal AOM	PP	Per Analysis Plan	414	271	0.36	0.23	34	(21, 45)
		Exclude all subsequent episodes of same serotype	374	245	0.31	0.21	34	(21, 44)
	ITT	Per Analysis Plan	467	322	0.32	0.22	32	(19, 42)
		Exclude all subsequent episodes of same serotype	405	288	0.27	0.19	29	(16, 40)

Tympanostomy Tube Placement

Table 12 presents summary data regarding the incidence of first tube placement in the FinOM Efficacy Study. As shown, nearly 20% of the children in the control group and 18.4% of the children in the Prevnar group had at least one procedure during the ITT follow-up period, resulting in an incidence of 0.12 and 0.11 per child year, respectively. In comparison to a reported incidence of 0.03 per child year in Finnish daycare attendees under 2 years of age,[27] the incidence of 0.12 per child year in the control group of this trial is unusually high. Because of this high incidence, further follow-up of tympanostomy tube placement in the study population was undertaken, as discussed in section 2.2.

Table 12: Tympanostomy Procedure (ITT Follow-Up) in FinOM Efficacy Trial Period

	HBV	Prevnar
No. of Randomized Subjects	831	831
No of Subjects Undergoing Tympanostomy Procedure	161 (19.4%)	153 (18.4%)
Incidence of First Tympanostomy Procedure (per person year)	0.12	0.11
Mean Age (mo.) of Procedure (interquartile range)	15.7 (4, 24)	15.9 (4, 24)
Mean Number of Prior AOM Episodes (interquartile range)	3.13 (2, 4)	3.21 (2, 4)
Mean Number of Prior AOM Visits (interquartile range)	4.48 (3, 5)	4.57 (4, 5)

2.2 Finnish Follow-Up Study

2.2.1 Description of Study Design, Definitions, and Outcome Variables for Tympanostomy Tube Placement

A Phase 4, follow-up study of the original FinOM Efficacy Study was designed to evaluate the long-term effects of the Prevnar vaccine on pneumococcal carriage and its serotype distribution, antibody persistence and otitis media morbidity. One of the objectives of highest interest was the study of the long-term effect of the Prevnar vaccine on the rates of tympanostomy tube placement. The discussion in this document will focus only on the information regarding tympanostomy tube placement in the Follow-up Study.

The children initially randomized to either the Prevnar or HBV arm (N=1662) in the FinOM Efficacy Study, having completed the follow-up through 24 months of age, and still living in the Tampere area were invited to a single follow-up visit between March and June 2001. All eligible children were age 4 to 5 years at the time of the planned follow-up visit. Nasopharyngeal sampling for major respiratory pathogens, blood and saliva sampling for antibody level, parental interview for otitis media history, and pneumatic otoscopy were performed at the single visit to the study clinic after parental/guardian informed consent. The FinOM Efficacy Study was unblinded in August 1999, and the information letters to parents disclosing the randomized vaccine were sent in late September 1999. The vaccination status of each child, therefore, was known to the parents/guardians, investigators, and study physicians and nurses at the time of the Follow-up Study visit. At the study visit it was documented using parental interview that the child had not received any pneumococcal vaccine since the completion of the FinOM Efficacy Study.

Definitions:

Tympanostomy tube placement was defined as placement of a tube in at least one ear or replacement of an extruded or occluded tube by a new one. Bilateral tube placements were considered as one event if the tubes were placed at the same operation. Repeated events in one individual study child at least one day apart were regarded as separate events.

Analysis Populations and Follow-up

- Analysis Population 1: children enrolled in the FinOM Follow-up Study (N=756).

The history of any tube placement procedure since the completion of the FinOM Efficacy Study at 24 months of age in this population was obtained initially through interviews of parents/guardians. Records of the procedures performed were then obtained from Tampere University Hospital (TAUH) or the three district hospitals, or private physician offices for verification. Thus, the case ascertainment in this population is expected to be complete.

- Analysis Population 2: all children enrolled in the original FinOM Efficacy Study and confirmed to be living in the TAUH district (N=1490 as of June 11, 2001).

Case ascertainment in this population was limited to a record search at Tampere University Hospital District (TAUH, and three district hospitals). All otological procedures performed up to June 11, 2001 were searched from the hospital discharge registry and the type of surgery was verified from the patient records. Procedures performed at private physician offices were not captured for children not enrolled in the Follow-up Study. Because the data on procedures performed at private physician offices were available for children enrolled in the Follow-up Study only (Analysis Population 1), these procedures performed outside TAUH were not included in the analyses performed for Analysis Population 2.

The data of the original FinOM Efficacy Study (N=1662 children) was used to ascertain the procedures performed between 2 months (day of enrollment) and 24 months (day of the close-out visit) of age for both analysis populations.

- Follow-up

The primary objective of the Follow-up Study was to evaluate the long-term effect of Prevnar from the age of 24 months to 4 to 5 years. In addition, the effect prior to 24 months was also of interest. The follow-up period for the analysis, therefore, will include both the efficacy trial intention-to-treat (ITT) follow-up period and the post trial long-term follow-up period.

The start of the follow-up period was the day the first dose of the study vaccine was administered. The end of follow-up period was the day of the visit for the Follow-up Study for Analysis Population 1 and June 11, 2001 for Analysis Population 2. The follow-up period ended at the discontinuation date for children who were discontinued from the efficacy trial follow-up (N=65) and ended at the 24-month visit for children who had moved out of the Tampere area since the completion of efficacy trial (N=107), since the day of relocation is not known.

Primary Analysis

The risk of tympanostomy tube placement during the long-term follow-up period was compared between the treatment groups in children enrolled in the FinOM Follow-up Study (Analysis Population 1). In order to take into account the biological variation between children in the history of tube placement, the analysis was based on all events during the entire follow-up period from first dose until 4 to 5 years of age rather than on the first event during the long-term follow-up. The efficacy of the vaccine in prevention of all events of tympanostomy tube placements was calculated separately for the FinOM Efficacy Study period (2 to 24 months) and for the long-term follow-up (from 24 months up to 4 to 5 years of age).

Secondary Analysis

The risk of tympanostomy tube placement during the long-term follow-up period was compared between the treatment groups in all children enrolled in the efficacy trial and confirmed to be living in the TAUH district (i.e. at risk for surgery in TAUH or the three district hospitals, Analysis Population 2).

2.2.2 Results of Analyses of Tympanostomy Tube Placement in the FinOM Follow-up Study

Table 13 presents the results of the primary analysis for the tympanostomy tube placement in the FinOM Follow-up Study. In Analysis Population 1, the Prevnar vaccine reduced the rate of tube placement by 12% (95% CI: -17, 34) during the period of 2 to 24 months of age. From the age of 24 months up to 4 to 5 years of age, the efficacy estimate of the Prevnar vaccine against tube placement was 39% (95% CI: 4, 61).

Table 14 presents the data for the secondary analysis. In Analysis Population 2, the Prevnar vaccine reduced the risk of tube placement by 4% (95% CI: -19, 23) in the 2 to 24 month age range and by 44% (95% CI: 19, 62) in the 24 month to 4 to 5 year age range.

Table 13: Tympanostomy Tube Placement in Children Enrolled in the FinOM Follow-up Study (Analysis Population 1)

	HBV	Prevnar	Vaccine efficacy* (95% CI)	P-value
Number Enrolled	353	403		
ITT Follow-up During FinOM Efficacy Study (Age: 2 months to 2 years)				
Number of Subjects with Events	84	82		
% Subjects with Events	23.8	20.3		
Number of Events	95	95	12%[a]	0.39
Rate of Events (/100 child yr)	14.8	12.9	(-17, 34)	
Long-term Follow-up Post FinOM Efficacy Study (Age: 2 years to ~ 4 to 5 years)				
Number of Subjects with Events	46[b]	33[c]		
% Subjects with Events	13.0	8.2		
Number of Events	57	40		
Rate of Events (/ 100 child yr)	5.7	3.5	39%	0.03
			(4, 61)	

a: Vaccine efficacy (Prevnar compared to HBV) calculated as 1-RR for each period estimated using Cox regression model with vaccine group as a covariate and an indicator variable for time period as a time-varying covariate.

b: 23 subjects had event(s) during the efficacy trial.

c: 17 subjects had event(s) during the efficacy trial.

Table 14: Tympanostomy Tube Placement in All Children Enrolled in the FinOM Efficacy Study Who Were at Risk (Analysis Population 2)

	HBV	Prevnar	Vaccine efficacy[a] (95% CI)	P-value
ITT Follow-up During FinOM Efficacy Study (Age: 2 months to 2 years)				
Number Included	831	831		
Number of Subjects with Events	161	153		
% Subjects with Events	19.3	18.4		
Number of Events	189	178	4%[a]	0.70
Rate of Events (/100 child yr)	12.7	12.0	(-19, 23)	
Long-term Follow-up Post FinOM Efficacy Study (Age: 2 years to ~ 4 to 5 years)				
Number Included	744	746		
Number of Subjects with Events	71[b]	46[c]		
% Subjects with Events	9.5	6.2		
Number of Events	92	53		
Rate of Events (/100 child yr)	4.1	2.4	44%[a]	<0.01
			(19, 62)	

a: Vaccine efficacy (Prevnar compared to HBV) calculated as 1-RR for each period estimated using Cox regression model with vaccine group as a covariate and an indicator variable for time period as a time-varying covariate.
b: 38 subjects had event(s) during the efficacy trial.
c: 19 subjects had event(s) during the efficacy trial.

2.3 Summary of the Results of the Finnish Studies

In summary, Prevnar was found in the FinOM Efficacy Study to be 57% efficacious against AOM caused by vaccine serotypes and 34% against all pneumococcal AOM, irrespective of serotype. These efficacy estimates were statistically significant. In addition, the efficacy against all vaccine-related serotypes combined was 51%. The efficacy varied by serotype from 84% for 6B to 25% for 19F, with statistically significant differences occurring for serotypes 6B, 14, and 23F. In addition, there was a statistically significant reduction in vaccine-related serotype 6A. The point estimate of efficacy increased with each subsequent dose through dose 3 from 21% after dose 1 to 57% after dose 3. There is a suggestion in this study of the possibility of partial replacement of vaccine serotypes with non-vaccine serotypes. However, based on this single

study, it is not possible to confirm that this is a real trend. For the placement of tympanostomy tubes, the rates of tube placement during the FinOM Efficacy Study appeared to be similar between treatment groups. However, long-term follow-up of children in the Follow-up Study revealed that there was a significant reduction of tube placements (39% - 44%) in children between the ages of 24 months and 4 to 5 years of age who had been immunized with Prevnar at 2, 4, 6 and 12 months of age.

3.0 Kaiser Efficacy Study (NCKP)

3.1 Description of Study Design, Definitions, and Outcome Variables

The D118-P8 study was performed at Kaiser Permanente in Northern California (NCKP) beginning in October 1995. The primary objective of this study was to assess the efficacy of the Prevnar vaccine against invasive pneumococcal disease compared to a control, investigational meningococcal group C conjugate vaccine (MnCC). Additional endpoints were effectiveness against otitis media and pneumonia, safety of the vaccines, and the ability of the vaccines to generate an immune response. Infants were immunized at 2, 4, 6, and 12 –15 months of age with either the Prevnar or MnCC vaccine. They also concurrently received either DTP-HbOC or DTaP and HbOC, as well as other routine immunizations (e.g. Hep B, OPV, IPV, MMR, Varicella).

For the assessment of otitis media, clinic and emergency room visits for AOM were ascertained using a database search of the NCKP Outpatient Summary Clinical Record database for all boxes checked for “acute otitis media” or “otitis media” by study physicians. Myringotomy and the culturing of MEF were not routinely performed. A limited number of samples were obtained from spontaneously-ruptured ears, but collection of fluid from ruptured ears was not routinely performed.

Key definitions that were employed in this study are as follows:

- **AOM**: No standardized definition for AOM across all clinics was used in this study. Clinic visits for AOM were ascertained using a database search of the NCKP Outpatient Summary Clinical Record database for all checked boxes for “acute otitis media” or “otitis media” on the NCKP clinical diagnosis forms.

- **AOM Episode**: An AOM episode was defined as a visit to a clinic at which time a diagnosis of otitis media was made, and it was at least 21 days following a previous AOM visit (at least 42 days, if the visit appointment was made > 3 days in advance).

- **Recurrent AOM**: A child was considered to have recurrent AOM if she/he had at least 3 otitis media episodes within a period of 6 months or at least 4 episodes within a period of 12 months.

- **Per-protocol follow-up:** A subject was considered vaccinated per-protocol for the otitis media analyses if the following criteria were met:

  - first dose ≥ 42 days of age
  - minimum 35 days and maximum 120 days between primary series doses
  - third dose given by 365 days of age
  - booster dose administered between 365 days (12 months) and 480 days (16 months)
  - at least 60 days from end of primary series to booster dose

Per-protocol follow-up began 14 days after the third dose of study vaccine in children vaccinated per-protocol and continued until they either dropped out of the health plan, they became 16 months of age without receipt of the booster dose, or until April 30, 1998 (database cut-off date).

- **Intent-to-treat Follow-up:** The intent-to-treat follow-up began immediately after each randomized subject received the first dose of study vaccine and continued until April 30, 1998 or the death of the subject.

The outcome variables assessed in this study were as follows:

Primary Analysis:

The primary objective was to compare the risk of all AOM episodes between the treatment groups during per-protocol follow-up (PP). The analysis plan, explicitly outlined prior to unblinding, was to perform the primary analysis first and to proceed to other analyses to further understand the vaccine effect only if the primary analysis showed statistically significant effect (at $p < 0.05$) on the reduction of risk of all AOM episodes. The hierarchy structure of endpoints was designed to maintain the overall type I error rate at 0.05 level.

Other Analyses and Endpoints (PP and ITT):

- First AOM episode
- Frequent AOM (≥ 3 episodes in 6 months or ≥ 4 episodes within 12 months)
- Tympanostomy tube placement
- Ruptured ears due to vaccine serotypes
- AOM visits

Exploratory Analyses and Endpoints

- Alternative definitions of frequent AOM
- Extended follow-up until April 20, 1999 (ITT) [Refer to Section 3.3]

3.2 Results for AOM Outcomes

A total of 34,146 children were randomized 1:1 to receive either Prevnar or the MnCC vaccine up to the data cut-off date of April 30, 1998. There were 17,070 children enrolled into the Prevnar group and 17,076 children enrolled into the MnCC group. Of these, 11,849 (69%) in the Prevnar group and 11,849 (70%) in the MnCC were included in the per-protocol analyses.

The results of the primary AOM analysis and several of the additional analyses are presented in Table 15. As shown, the overall incidence of AOM episodes in the per-protocol population was reduced from 1.72 episodes per person year to 1.60 episodes per person year, a 7% reduction. This reduction is statistically significant ($p<0.0001$), with a 95% confidence interval from 4% to 10%. Vaccine effectiveness for the other endpoints in the per-protocol population ranged from a 5% reduction for risk of first episode to a 20% reduction in the incidence of first tympanostomy tube placement. Similar results were obtained in the ITT population. For all of these endpoints, the differences between treatment groups were statistically significant.

Table 15: Summary Of Results of Primary and Secondary Analyses for AOM in NCKP Study

Outcome Variable	Follow-up Period	Number		Rate/person year		Vaccine Efficacy (%)	
		Prevnar	MnCC	Prevnar	MnCC	Estimate	95%CI
All AOM Episodes	PP	16124	17405	1.60	1.72	7	(4, 10)
	ITT	25590	27199	1.29	1.37	6	(4, 9)
First AOM Episode	PP	7126	7411	0.65	0.67	5	(2, 8)
	ITT	10112	10394	0.47	0.49	5	(2, 7)
All AOM Visits	PP	22478	24914	2.05	2.25	9	(6, 12)
	ITT	35031	38010	1.64	1.78	8	(5, 11)
				Rate/ 100 person years	**Rate/ 100 person years**		
Frequent AOM Episodes	PP	1647	1809	16.4	17.9	9	(3, 15)
	ITT	2612	2839	12.3	13.3	9	(4, 14)
First Tympanostomy Tube Placement	PP	157	198	1.43	1.79	20	(2, 35)
	ITT	192	240	0.90	1.13	21	(4, 34)

Results of the cultures of spontaneously-draining, ruptured eardrums accrued through November, 1998 are presented in Table 16. A total of 20 cases of ruptured eardrums with vaccine-serotype isolates were seen in the intent-to-treat population, with 13 of these included in the per-protocol analysis. The vaccine efficacy estimates were not statistically significant and the 95% confidence intervals covered a wide range, reflecting the small sample size and low statistical power for this endpoint.

Table 16: Analysis of Vaccine Efficacy Against Ruptured Ear Drums due to Pneumococcal Infection in Cases Accrued Through November 6, 1998 (PP and ITT)

Ruptured Eardrum	Number of Cases		Vaccine Efficacy Estimates (%)	(95% confidence interval)
Cases through November 6, 1998				
Vaccine Serotypes	**Prevnar**	**MnCC**		
PP	4	9	56	(-59, 90)
ITT	6	14	57	(-19, 86)
All Serotypes				
PP	5	13	62	(-15, 89)
ITT	7	18	61	(2, 86)

Results of Exploratory Analyses

Exploratory analyses were performed using two amended definitions of recurrent otitis media with increasing severity: 1) at least 4 episodes within 6 months or 5 episodes within 12 months, 2) at least 5 episodes within 6 months or 6 episodes within 12 months.

For the analysis of more severe cases of recurrent otitis media, as shown in Table 17, the vaccine effect appeared to increase with increasingly more serious otitis media endpoints.

Table 17: Cases of More Severe Recurrent Otitis

Frequent Otitis Definition	Population	Number of Children With Frequent Episodes		Vaccine Efficacy (%)	
		Prevnar	MnCC	% Reduction (95% CI)	95% CI
≥3 episodes in 6 mo. or 4 in 12 mo.	PP	1647	1809	9	(3, 15)
	ITT	2612	2839	9	(4, 14)
≥4 episodes in 6 mo. or 5 in 12 mo.	PP	597	679	12	(2, 21)
	ITT	1115	1231	10	(2, 17)
≥5 episodes in 6 mo. or 6 in 12 mo.	PP	188	246	23	(7, 36)
	ITT	414	471	12	(0, 23)

3.3 Description and Results of Extended Follow-Up of Kaiser Population

The cut-off date for the initial analyses of otitis media data presented above was April 30, 1998. As the study remained blinded until April 20 1999, subsequent analyses of all AOM episodes, first AOM episode, tube placement, all AOM visits, frequent AOM and ruptured eardrums during the intent-to-treat follow-up were performed up to April 20, 1999. These results are presented in Table 18. As shown, the results are quite consistent with the estimates using the April 1998 cut-off date.

Table 18: Efficacy Analyses for AOM During Intent-to-treat Follow-up - All Data of NCKP Trial through April 20, 1999

	ITT Follow-up					
	Number of Subjects		Number of Events		Risk Reduction Estimate (%) (95% CI)	
	April 30, 1998	April 20, 1999	April 30, 1998	April 20, 1999	April 30, 1998	April 20, 1999
All AOM Episodes	34146[a]	37866[b]	52789	84978	6.4 (3.9, 8.7)	5.9 (3.8, 7.9)
First AOM Episode	34146	37866	20506	27343	4.9 (2.3, 7.5)	4.4 (2.1, 6.7)
All AOM Clinic Visits	34146	37866	73041	116636	7.8 (5.2, 10.5)	7.0 (4.8, 9.2)
Frequent AOM	34146	37866	5451	12252	9.2 (4.3, 13.9)	10.9 (7.7, 14.0)
First Tube Placement	34146	37866	432	751	20.6 (4.0, 34.3)	23.2 (11.3, 33.5)
Ruptured Ear Drum due to Vaccine Serotypes	34146	37866	20[c]	24	57.1 (-18.7, 86.5)	66.7 (12.3, 89.2)

a: Prevnar: 17070; MnCC: 17076
b: Prevnar: 18925; MnCC: 18941
c: Original follow-up of ruptured ear drum ended November 6, 1998 when the original AOM database was unblinded for analysis.

3.4 Summary of Results of NCKP Study

In summary, a statistically significant risk reduction was seen in Prevnar recipients in this large-scale study across all variables assessed, except ruptured ears. For the primary AOM outcome, all episodes, there was a 7% reduction in the per-protocol population. The estimated risk reduction for other variables in the PP population ranged from 5% for the risk of a first episode to 20% for the risk of first tympanostomy tube placement. For the small set of data on ruptured ears, the efficacy in the PP population against vaccine serotype isolates was 56%. The efficacy estimates in the ITT population for the follow-up analyses (through April 20, 1999) were consistent with those in the initial analyses (through April 30, 1998), and the ruptured ear endpoint reached statistical significance.

Discussion and Conclusions

As shown by the data previously presented, Prevnar clearly reduces the frequency of acute otitis media in children. In the FinOM Efficacy Study, the efficacy of the vaccine against all culture-confirmed AOM episodes caused by the 7 vaccine serotypes in the PP population was 57% (95% CI: 44, 67). In addition, the vaccine was also found to be cross protective against vaccine-related pneumococcal serotypes, with a combined efficacy of 51% (95% CI: 27, 67). For all pneumococcal AOM episodes, regardless of serotype, the efficacy of the vaccine was 34% (95% CI: 21, 45). When using a more general endpoint of all AOM episodes, regardless of causative etiologic agent, the vaccine was found to reduce the incidence by 6% (95% CI: –4, 16) in the FinOM study. These data were supported by the data resulting from the NCKP study, in which there was a 7% reduction (95% CI: 4, 10) in all AOM episodes, even though the definition of an episode was slightly different and the study was conducted in a different geographical setting. In addition, while the data set for ruptured ear isolates due to pneumococcal infection was very small in NCKP, the 56% reduction in isolates due to vaccine serotypes was similar to the 57% seen in the FinOM Efficacy Study.

It has been reported that approximately 50% of all US children will have had at least 3 episodes of otitis media by the age of three years and that recurrent otitis media has its onset almost exclusively before 2 years of age.[5] In the FinOM Efficacy and NCKP studies, Prevnar was found to be effective in reducing the risk of recurrent otitis media, defined as at least 3 episodes in a 6-month period or at least 4 episodes in a 12-month period. In the FinOM study, there was a 16% risk reduction (95% CI: –6, 35) in the PP population and a 9% reduction (95% CI: –12, 27) in the ITT population. This was similar to that seen in the NCKP study, in which there was a 9% reduction in both the PP (95% CI: 3, 15) and ITT (95% CI: 4, 14) populations. As an exploratory analysis, when the definition of recurrent AOM in the NCKP study was changed to a more severe definition to include children with at least 4 episodes in 6 months or 5 in 12 months, the reduction was 12% (95% CI: 2, 21) in the PP population. When utilizing an even more severe definition of recurrent AOM of at least 5 episodes in 6 months or 6 in 12 months, the reduction was 23% (95% CI: 7, 36) in the PP population. The trend was toward an increasing vaccine effect with increasingly more serious recurrent OM endpoints.

An additional endpoint supporting the otitis media indication was the placement of tympanostomy tubes in children. In the NCKP trial, there was a significant reduction (20%, 95% CI: 2, 35 in PP and 21%, 95% CI: 4, 34 in ITT) in the first ear tube placement surgeries in children immunized with Prevnar. However, the analysis of ear tube placement data from the

FinOM Efficacy Study found little effect, if any, of Prevnar on the incidence of ear tube placement. One possible reason for the different results could be the over 10-fold higher rate of ear tube surgery during the FinOM Efficacy Study compared to the NCKP study. This disparity in surgery rates is in sharp contrast to the incidence rates of AOM during the two studies, which did not differ markedly (1.24 episodes per child year in FinOM vs. 1.72 per child year in NCKP). The relatively high rate of tube placement in the FinOM study may be the result of an active treatment strategy employed in the study sites that may have resulted in children receiving treatment at an earlier stage of disease due to quick access to medical care. In the NCKP study, however, children were followed in the normal routine practice of the health care organization. The FinOM Follow-up study further assessed the impact of Prevnar on long-term ear tube placement in children who participated in the original FinOM Efficacy Study, but who had returned to the normal rate of tube placement. Prevnar significantly reduced the incidence of ear tube placements by 39% (95% CI: 4, 61) to 44% (95% CI: 19, 62) during the period of 24 months to 4-5 years of age, supporting the results of the NCKP study.

Data from the FinOM Efficacy Study suggest that vaccination with Prevnar may be associated with an increased number of AOM cases caused by non-vaccine serotypes. The replacement of AOM cases was only partial, in that a net decrease on the order of 34% of pneumococcal AOM cases remained apparent in the vaccinated group in Finland, translating into net decreases of 5-7% in all AOM episodes in Finland (not significant) that mirrored the significant decrease previously seen at NCKP. It is also reassuring that there has been no evidence of any increase in non-vaccine serotype invasive disease thus far in the NCKP invasive disease efficacy study, the NCKP post-marketing surveillance, or nationwide surveillance by the CDC.[1, 2, 26]

In conclusion, Prevnar is highly effective in reducing the incidence of AOM caused by pneumococcal vaccine serotypes and related serotypes. Because the pneumococcus is one of many causative agents responsible for AOM, the impact of immunization on all episodes, when expressed as a percentage of all cases, is relatively small. However, because of the large number of AOM episodes that occur in children, immunization with Prevnar could have a significant public health impact by reducing the number of episodes. To put this effect into perspective, by assuming that there are approximately 20 million episodes of AOM each year in the US in children under 59 months of age, approximately 1.1 to 1.4 million episodes will be prevented each year by immunization with Prevnar.[28] This decrease in disease burden would likely be associated with a decrease in associated antibiotic prescriptions. For ear tube surgeries, over 60,000 surgeries will be prevented based on the estimate that over 300,000 ear tube placements occur each year in US in children under 59 months of age.[28] This substantial public

health effect represents an important attribute of the vaccine that should be explicitly described and communicated to providers and parents within the product labeling. In addition, the pneumococcus has been reported to be disproportionately responsible for more severe AOM episodes, less likely to resolve spontaneously and to be associated with higher rates of fever relative to other pathogens.[10, 11, 29] This amplifies the significance of the impact of Prevnar on the health of children. While an increase in non-vaccine serotype AOM cases with Prevnar vaccine during the FinOM trial has been suggested, it is impossible to predict with a high degree of confidence the extent, if any, of replacement disease caused by selective pressure by the vaccine over time. However, preliminary clinical evidence suggests that replacement, if it occurs, is not complete. The enhanced surveillance of invasive pneumococcal disease being conducted by the CDC and at NCKP may provide the best data on the magnitude and clinical impact of any such replacement.

Appendix 1: Statistical Methods

I. Introduction

The evaluations of the effect of Prevnar on acute otitis media were based on three studies: 1. FinOM Efficacy Study, 2. FinOM Follow-up Study, and 3. Northern California Kaiser-Permanente (NCKP) efficacy study. The details of the statistical hypothesis testing structure, analysis methods, and significance levels of the AOM outcomes of each study are provided in this appendix.

II. Structure of Testing Framework and Type I Error Rates

II.1 Finnish Otitis Media Efficacy Study (FinOM)

II.1.1 Analyses Included in the sBLA Submission

The FinOM study provides the pivotal efficacy data of Prevnar against acute otitis media. Several efficacy outcomes were considered clinically important. To control the experiment-wise type I error rate while investigating the vaccine effect on multiple endpoints, the following hierarchy testing structure was set up *a priori*.

1. Primary Efficacy Variable: All AOM episodes due to vaccine serotypes

The null hypothesis of no vaccine efficacy with respect to the primary efficacy variable was to be tested at significance level of 0.05. If the p-value was > 0.05, no other efficacy variable would be formally tested for vaccine effect. The strength of evidence of vaccine efficacy in other variables would only be evaluated if the primary variable showed statistically significant vaccine effect. Thus, the trial can have a positive outcome only if the a priori primary efficacy variable is significant at α level of 0.05.

2. Other Efficacy Variables:

The null hypothesis of no effect was tested for each of the following *a priori* specified efficacy variables once the vaccine efficacy in the primary variable was shown to be significant at α level of 0.05.

- First AOM episode due to vaccine serotype
- Subsequent vaccine serotype episodes
- Vaccine serotype episodes by dose

- Culture-confirmed pneumococcal AOM episodes regardless of serotype
- Pneumococcal AOM episodes as determined by either culture or PCR
- AOM episodes with MEF regardless of etiology
- AOM episodes regardless of etiology
- Recurrent AOM

The marginal P-value of each individual test, irrespective of the results of other variables in this category, was obtained (Section IV below). In order to maintain the category-wise type I error rate at a given level, the marginal P-values need to be interpreted with multiple comparisons taken into consideration. A simple but over-conservative approach (over-conservative due to the correlation of the outcomes) is to apply Bonferroni adjustment to the marginal P-values. For example, if each individual test is considered at a level of 0.006, the category-wise α will be capped at 0.05.

3. Post-Hoc Tests:

The null hypothesis of no vaccine effect was tested for the following group of variables after a significant vaccine effect in all culture-confirmed pneumococcal AOM was observed to further understand the composition of the vaccine effect in vaccine-serotype AOM and all pneumococcal AOM.

- AOM episodes due to vaccine-related serotypes
- AOM episodes due to serotypes unrelated to vaccine serotypes
- AOM episodes due to individual serotypes in the vaccine serogroups

Although these variables were not pre-specified in the analysis plan, they were closely related to the primary variable of all vaccine-serotype AOM and/or the secondary variable of all pneumococcal AOM (culture-confirmed) and were only evaluated after a significant vaccine effect was seen in these two variables. The overall experiment-wise α for the trial and the category-wise α of Category 2 above (other efficacy variables) were intact with the cascading test structure. Within this category itself, however, the marginal P-values of individual tests need to be interpreted with multiple comparisons taken into consideration so the category-wise α can be maintained at a given level. For example, if each of the 14

individual tests in this category is considered at a level of 0.0035, the category-wise α will be capped at 0.05 using Bonferroni adjustment.

II.1.2 Post-Submission Analyses

The following post-hoc statistical analyses were performed per CBER's request during the review period to assess the influence of potential demographic or baseline risk factors and to explore the robustness of the efficacy conclusions with respect to the definition of an episode.

- Covariate analysis to test the significance of the main effect of several covariates and the interaction between each of the covariate with vaccine group on vaccine-serotype AOM episodes, culture-confirmed pneumococcal AOM episodes, AOM episodes with MEF, and AOM episodes regardless of etiology. The covariates assessed include AOM history prior to enrollment, gestational age, birth weight, gender, daycare attendance, breastfeeding, and household smoking. The main effect estimates the effect of the covariate on the overall incidence of the AOM endpoint while the interaction between the covariate and vaccine group measures the difference of vaccine effect in different subgroups defined by the covariate.

- Vaccine efficacy in vaccine-serotype AOM and all culture-confirmed pneumococcal AOM with an alternative definition of an episode. The alternative definition excludes all subsequent episodes due to a given serotype within a child.

These post-submission analyses were performed for the purpose of verifying the robustness of the conclusions derived from the original analyses. No specific control for multiple tests was set in place. The marginal P-values should be interpreted with the considerations that over fifty statistical tests were performed within this category.

Descriptive statistics on the incidence of first tympanostomy tube placement during the efficacy trial were also obtained as one of the post-submission evaluations. Due to the unusually high incidence in both groups, as compared to the common practice reported in Finland and the US,

the ability to generalize tube placement as an efficacy endpoint seems questionable and, therefore, no formal statistical test was performed.

II.2 Finnish Otitis Media Long-Term Follow-up Study

The data from a long-term follow-up study of the children who participated in the original Finnish efficacy trial became available post submission. As this long-term study is not an intervention study with intense clinical follow-up, it is believed that the treatment of AOM returned to the normal practice in Finland. The long-term vaccine effect on the risk of tympanostomy tube placement in this setting was assessed. Two endpoints were tested based on the following hierarchy structure to control the experiment-wise α of this separate study:

1. Primary Test of Long-term Effect on Tube Placement:

- Vaccine effect on the risk of tympanostomy tube placement during the long-term follow-up period from 24 months of age to 4 to 5 years of age in children who enrolled in the long-term follow-up study. Events were captured in this group through parental interview and hospital records search. As the primary variable, this endpoint was tested at α level of 0.05.

2. Secondary Test of Long-term Effect on Tube Placement:

- Vaccine effect on the risk of tympanostomy tube placement during the long-term follow-up period from 24 months of age to 4 to 5 years of age in all of the children who participated in the original efficacy trial and still resided in the same geographic area. Events were captured in this group by hospital records search only. As the single variable in the secondary category, this endpoint was tested at α level of 0.05 once a significant effect in the primary variable was observed.

As the tube placement events that occurred during the age from 2 months to two years may affect the risk later in the same individual, the analysis of the long-term vaccine effect took into account the tube placement events history, including the efficacy trial period, within individuals (described below in Section III). As a result, the analysis model also provided an estimate of the vaccine effect during the efficacy trial period. The P-value associated with the estimate for the efficacy trial period was considered of ancillary nature as the ability to generalize tube placement as an efficacy endpoint during the efficacy trial period is unclear.

II.3 Northern California Kaiser-Permanente Efficacy Study (NCKP)

The NCKP study was designed to first evaluate the efficacy of Prevnar against invasive pneumococcal disease. As such, the primary variable of the trial was invasive pneumococcal disease due to vaccine serotypes. A hierarchy testing structure was also set up to evaluate several other clinically important endpoints while maintaining the overall type I error rate. The vaccine effect on acute otitis media (AOM) was to be evaluated only if a significant vaccine effect at α level of 0.05 was seen in the primary efficacy variable of invasive disease. Thus, the experiment-wise α for the trial can be kept at 0.05 level. Within the category of AOM variables, a further hierarchy testing structure was set up *a priori* to control the category-wise type I error rate.

II.3.1 Analyses Included in the sBLA Submission

1. Primary AOM Variable: All AOM episodes

The null hypothesis of no vaccine effect was tested with respect to the primary AOM variable at significance level of 0.05. If the p-value was > 0.05, no other AOM variable would be formally tested for vaccine effect. The strength of evidence of vaccine effect in other AOM variables would only be evaluated if the primary AOM variable showed statistically significant vaccine effect.

2. Secondary AOM Variables:

The null hypothesis of no effect was tested for each of the following a priori specified AOM variables once the vaccine efficacy in the primary AOM variable was shown to be significant at α level of 0.05.

- First AOM episode
- Frequent Otitis Media
- Tympanostomy tube placement
- Ruptured ear drum due to vaccine serotypes
- All clinic visits for otitis media

The marginal P-value of each individual test, irrespective of the results of other variables in this category, was obtained (Section III below). In order to maintain the category-wise type I error rate at a given level, the marginal P-values need to be interpreted with multiple

comparisons taken into considerations. If each individual test is considered at a level of 0.01, the category-wise α will be capped at 0.05 using Bonferroni adjustment.

II.3.2 Post-Submission Analyses

The AOM database from the NCKP study contains data accrued from September 1995 through April 30, 1998. The *a priori* decision of end date allowed the AOM data to be unblinded and analyzed, with excellent statistical power, at the same time as the invasive disease cases. Blinded clinical follow-up for the study, however, continued until April 20, 1999. Post-submission analyses of all above primary and secondary AOM variables during ITT follow-up were performed, per CBER's request, on the extended database containing data accrued through April 20, 1999 to confirm the conclusions derived from the original analyses. No specific control for multiple tests was set in place. As the study enrollment was stopped in August 1998, the extended follow-up database contains a greater proportion of follow-up time in older children than that in the original database.

III. Statistical Methods

III.1 Finnish Otitis Media Efficacy Study (FinOM)

A generalized Cox regression model proposed by Andersen and Gill[30] was used to analyze AOM episodes. The model evaluates the effect of explanatory variables on cumulative number of events over any given amount of follow-up time. A relative risk estimate comparing the risk between groups can be obtained using Cox's partial likelihood method. In this situation the model may be presented either in terms of hazard functions or mean numbers of events (Nelson-Aalen plots). The assumption of proportional hazards was checked by inspection of the plots of hazard rate or mean events. The model provides consistent parameter estimates in the presence of intra-subject correlation between recurrent events. However, the variance of the parameter estimate could be underestimated. A GEE type of sandwich estimate was used to provide a robust variance estimate in the presence of clustering.[31] A simple model with vaccine group as the only explanatory variable was used to analyze all AOM variables except the first vaccine-serotype event and the subsequent vaccine-serotype events. A single model with vaccine group as an explanatory variable, a time-varying covariate to indicate whether a subject has had the first episode at the given time point and the interaction of vaccine group and the covariate was used to analyze the first episode and subsequent episode. Separate vaccine effect estimates for the first and subsequent events can be derived from the model.

The Andersen-Gill model was also used for the post-submission covariate analyses for evaluating the effect of demographic characteristics. Each of the covariates and its interaction with vaccine group were included in the model. Due to the total number of parameters and the sparse data in the subgroups defined by low birth weight, low gestational age, and daycare before 6 months of age, an analysis of covariance model containing all the covariates and interactions simultaneously presents computational difficulty. The analysis was performed with one covariate at a time. Since no significant interaction was found between any of the covariates with vaccine group, an analysis with only the main effects in the model was performed to obtain covariate-adjusted vaccine effect estimate.

III.2 Finnish Otitis Media Long-Term Follow-up Study

An Andersen-Gill model was also used for the analysis of tympanostomy tube placement in the FinOM Follow-Up Study. As earlier tube placement may affect the risk later within individuals, the Andersen-Gill Model, therefore, was based on all tube placement events since the beginning of FinOM efficacy trial through the end of the long-term follow-up. In addition to vaccine group as an explanatory variable, an indicator variable which identifies the time period (efficacy trial period or long-term follow-up period) when each event occurred was also included in the model as a time-varying covariate. The interaction between vaccine effect and the time period covariate provides different vaccine efficacy estimates for the two different time periods. The sandwich estimate method was also used to obtain robust estimates of the variances for the regression parameters.

III.3 Northern California Kaiser-Permanente Efficacy Study (NCKP)

Similar to the FinOM trial, a simple Andersen-Gill model with vaccine group as the only explanatory variable and the sandwich estimate of the variance for regression parameter was used to analyze recurrent event data from the NCKP trial including all AOM episodes and all AOM visits. Single event data including first episode, frequent otitis, and first tympanostomy tube placement were analyzed using original Cox proportional hazard model. The ruptured ear drum data were analyzed using the exact binomial test.

IV. Significance Levels and Strength of Evidence

The marginal P-values of the individual tests in each of the three trials are tabulated in the tables below. As discussed above, the P-values should be interpreted within the respective testing structure framework.

1. FinOM Efficacy Study
   - Analyses included in the sBLA submission: Tables A1-A2
   - Post-submission covariate analyses: Table A3
   - P-values from the post-submission analyses that excluded all subsequent events due to a given serotype are not tabulated here as the point and interval estimates for vaccine were similar to that from the original analyses.

2. FinOM Long-Term Follow-up Study
   - Analyses of tube placement : Table A4

3. NCKP Efficacy Study
   - Analyses included in the sBLA submission: Tables A5-A6
   - Post-submission analyses: Table A7

4. Similar Outcome Variable in Finland and Northern California
   - Similar outcome variables in Finland and Northern California including All AOM regardless of etiology, recurrent or frequent AOM, and tympanostomy tube placement: Table A8

Table A.1 : Summary of PP Analysis Results in the FinOM Efficacy Study

	Vaccine Efficacy		
	Estimate	**95%CI**	**P-value[a]**
Primary Efficacy Variable			
AOM due to vaccine serotypes	57%	(44%, 67%)	< 0.0001
Other Efficacy Variables			
First AOM Episode due to Vaccine Serotype	52%	(39%, 63%)	< 0.0001
Subsequent AOM Episode (after first VT episode) due to Vaccine Serotype	45%	(5%, 69%)	0.0329
All culture-confirmed pneumococcal AOM episodes	34%	(21%, 45%)	< 0.0001
Pneumococcal AOM episodes as determined by culture or PCR	20%	(7%, 31%)	0.0030
AOM episodes with MEF	7%	(-5%, 17%)	0.2448
AOM episodes regardless of etiology	6%	(-4%, 16%)	0.2353
Recurrent AOM	16%	(-6%, 35%)	0.1294
Post Hoc Variables			
AOM due to vaccine related serotypes	51%	(27%, 67%)	0.0005
AOM due to other than vaccine related serotypes	-34%	(-81%, 0%)	0.0597
AOM due to			
serotype 6B	84%	(62%, 93%)	< 0.0001
serotype 14	69%	(20%, 88%)	0.0150
serotype 23F	59%	(35%, 75%)	0.0002
serotype 18C	58%	(-45, 83%)	> 0.05
serotype 9V	54%	(-48%, 86%)	> 0.05
serotype 4	49%	(-176%, 91%)	> 0.05
serotype 19F	25%	(-14%, 51%)	> 0.05
serotype 6A	57%	(24%, 76%)	0.0037
serotype 9N	75%	(-24%, 95%)	> 0.05
serotype 18B	-103%	(-2130%, 82%)	> 0.05
serotype 19A	34%	(-26%, 65%)	> 0.05
serotype 23A	75%	(-151%, 97%)	> 0.05

a: Marginal P-value for individual test based on Cox-regression with robust estimate of variance.

Table A.2: Summary of ITT Analysis Results in the FinOM Efficacy Trial

	Vaccine Efficacy		
	Estimate	**95%CI**	**P-value[a]**
Primary Efficacy Variable			
AOM due to vaccine serotypes	54%	(41%, 64%)	< 0.0001
Other Efficacy Variables			
First AOM Episode due to Vaccine Serotype	48%	(34%, 59%)	< 0.0001
Subsequent AOM Episode (after first VT episode) due to Vaccine Serotype	49%	(20%, 67%)	0.0033
All culture-confirmed pneumococcal AOM episodes	32%	(19%, 42%)	< 0.0001
Pneumococcal AOM episodes as determined by culture or PCR	18%	(5%, 29%)	0.0066
AOM episodes with MEF	4%	(-7%, 14%)	0.4347
AOM episodes regardless of etiology	4%	(-7%, 14%)	0.4215
Recurrent AOM	9%	(-12%, 27%)	0.4104
Post Hoc Variables			
AOM due to vaccine related serotypes	44%	(20%, 62%)	0.0018
AOM due to other than vaccine related serotypes	-39%	(-86%, -3%)	0.0289
AOM due to			
serotype 6B	80%	(60%, 90%)	< 0.0001
serotype 14	74%	(34%. 90%)	0.0046
serotype 23F	62%	(41%, 75%)	< 0.0001
serotype 18C	61%	(2%, 85%)	0.0433
serotype 9V	45%	(-66%, 85%)	> 0.05
serotype 4	50%	(-172%, 91%)	> 0.05
serotype 19F	10%	(-32%, 39%)	> 0.05
serotype 6A	52%	(17%, 72%)	0.0085
serotype 9N	78%	(-6%, 95%)	> 0.05
serotype 18B	-101%	(-2108%, 82%)	> 0.05
serotype 19A	21%	(-40%, 56%)	> 0.05
serotype 23A	75%	(-149%, 97%)	> 0.05

a: Marginal P-value for individual test based on Cox-regression with robust estimate of variance.

Table A3: Significance Levels (P-Values) of the Main Effect of Covariates and the Interactions with Vaccine in Andersen-Gill Models – Post-Submission Analyses of FinOM Efficacy Trial

	P-Values of Main Effect and Interaction with Vaccine													
	Gender		AOM Prior to Enrollment		Gestational Age		Birth Weight		Daycare Attendance		Breastfeeding		Household Smoking	
	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]	Main[a]	Int.[a]
AOM due to Vaccine Serotypes														
PP	0.03	0.56	< 0.01	0.69	0.59	0.95	0.17	0.07	< 0.01	0.46	0.11	0.09	0.56	0.11
ITT	0.01	0.21	< 0.01	0.84	0.96	0.56	0.09	0.06	< 0.01	0.37	0.33	0.64	0.86	0.17
Culture-confirmed Pneumococcal AOM														
PP	0.08	0.95	< 0.01	0.89	0.77	0.75	0.09	0.26	< 0.01	0.32	0.31	0.25	0.14	0.21
ITT	0.05	0.81	< 0.01	0.81	0.45	0.28	0.04	0.12	< 0.01	0.23	0.76	0.89	0.24	0.26
AOM with MEF														
PP	< 0.01	0.83	< 0.01	0.34	0.46	0.95	0.04	0.74	< 0.01	0.83	0.93	0.80	0.22	0.16
ITT	< 0.01	0.96	< 0.01	0.39	0.45	0.70	0.04	0.46	< 0.01	0.85	0.20	0.28	0.16	0.07
AOM Regardless of Etiology														
PP	< 0.01	0.72	< 0.01	0.14	0.36	0.81	0.04	0.67	< 0.01	0.99	0.81	0.98	0.21	0.13
ITT	< 0.01	0.98	< 0.01	0.19	0.35	0.46	0.04	0.39	< 0.01	0.98	0.19	0.32	0.18	0.07

a: Main = main effect; Int. = interaction with vaccine. Due to the total number of parameters and the sparse data in the subgroups defined by low birth weigh, short gestational age, and daycare before 6 months of age, an analysis of covariance model contains all the covariates and interactions presents computational difficulty. The analysis was performed with one covariate at a time.
Values for each variable:
Daycare: 0 = no daycare / 1 = any type of daycare
Gestational age: 0 = greater than or equal to 37 weeks / 1 = less than 37 weeks
Birth weight: 0 = greater than or equal to 2.5 kg / 1 = less than 2.5 kg
Previous AOM: 0 = no previous AOM / 1 = previous AOM
Gender: 0 = female / 1 = male
Breastfeeding: 0 = no breastfeeding / 1 = breastfeeding
Smoking: 0 = no smoking / 1 = any smoking

Table A.4 : Summary of Tube Placement Results in FinOM Long-Term Follow-up Study

	Vaccine Efficacy		
	Estimate	**95%CI**	**P-value[a]**
Primary Tube Placement Variable			
All tube placement events from the end of efficacy trial through 4 to 5 years of age in children enrolled in the long-term follow-up study	39%	(4%, 61%)	0.03
Secondary Tube Placement Variable			
All tube placement events at Tampere University Hospital District (TAUH) from the end of efficacy trial through 4 to 5 years of age in all children enrolled in the original efficacy trial and still resided in the TAUH district	44%	(19%, 62%)	< 0.01
Ancillary Tests			
All tube placement events from 2 months of age through the end of efficacy trial in children enrolled in the long-term follow-up study	12%	(-17%, 34%)	0.39
All tube placement events from 2 months of age through the end of efficacy trial in all children enrolled in the original efficacy trial and still resided in the TAUH district	4%	(-19%, 23%)	0.70

a: Marginal P-value for individual test based on Cox-regression with robust estimate of variance.

Table A.5 : Summary of PP Analysis Results in the NCKP Efficacy Study

	Vaccine Efficacy		
	Estimate	**95%CI**	**P-value[a]**
Primary AOM Variable			
All AOM episodes	7%	(4%, 10%)	< 0.0001
Secondary AOM Variables			
First AOM Episode	5%	(2%, 8%)	0.0008
Frequent AOM	10%	(3%, 15%)	0.0035
First tympanostomy tube placement	20%	(2%, 35%)	0.0335
Ruptured ear drum with vaccine serotype isolates	56%	(-59%, 90%)	0.2670
All AOM Visits	9%	(6%, 12%)	< 0.0001

a: Marginal P-value for individual test based on Cox-regression with robust estimate of variance.

Table A.6 : Summary of ITT Analysis Results in the NCKP Efficacy Study

	Vaccine Efficacy		
	Estimate	**95%CI**	**P-value[a]**
Primary AOM Variable			
All AOM episodes	6%	(4%, 9%)	< 0.0001
Secondary AOM Variables			
First AOM Episode	5%	(2%, 8%)	0.0003
Frequent AOM	9%	(4%, 14%)	0.0004
First tympanostomy tube placement	21%	(4%, 34%)	0.0171
Ruptured ear drum with vaccine serotype isolates	57%	(-19%, 87%)	0.1150
All AOM Visits	8%	(5%, 11%)	< 0.0001

a: Marginal P-value for individual test based on Cox-regression with robust estimate of variance.

Table A.7 : Summary of ITT Analysis Results in the NCKP Efficacy Study – Post-Submission Analyses of Extended Follow-up through April 20, 1999

	Vaccine Efficacy		
	Estimate	**95%CI**	**P-value[a]**
Primary AOM Variable			
All AOM episodes	6%	(4%, 8%)	< 0.0001
Secondary AOM Variables			
First AOM Episode	4%	(2%, 7%)	0.0002
Frequent AOM	11%	(8%, 14%)	< 0.0001
First tympanostomy tube placement	23%	(11%, 34%)	0.0003
Ruptured ear drum with vaccine serotype isolates	67%	(12%, 89%)	0.1150
All AOM Visits	7%	(5%, 9%)	< 0.0001

a: Marginal P-value for individual test based on Cox-regression with robust estimate of variance.

Table A.8 : Summary of Results of Similar Outcome Variables in Finland and Northern California

	Vaccine Efficacy		
	Estimate	**95%CI**	**P-value[a]**
All AOM episodes regardless of etiology (ITT)			
NCKP – Primary variable	6%	(4%, 9%)	< 0.0001
FinOM – Secondary variable	4%	(-7%, 14%)	0.4215
Frequent or Recurrent AOM (ITT)			
NCKP – Secondary variable	9%	(4%, 14%)	0.0004
FinOM – Secondary variable	9%	(-12%, 27%)	0.4104
Tympanostomy tube placement (ITT)			
NCKP			
First event in all children – Secondary variable	21%	(4%, 34%)	0.0171
First event in all children during extended follow-up with greater proportion of follow-up time in older children	23%	(11%, 34%)	0.0003
FinOM			
All events between 2 years and 4 to 5 years of age in children enrolled in the long-term study – Primary variable for the long-term study	39%	(4%, 61%)	0.03
All events between 2 years and 4 to 5 years of age in all children enrolled in the original efficacy trial and still resided in the area – Secondary variable for the long-term study	44%	(19%, 62%)	< 0.01
All events during efficacy trial period in children enrolled in the long-term study – Ancillary variable for the long-term study	12%	(-17%, 34%)	0.39
All events during efficacy trial period in all children enrolled in the original efficacy trial and still resided in the area – Ancillary variable for the long-term study	4%	(-19%, 23%)	0.70

a: Marginal P-value for individual test based on Cox-regression with robust estimate of variance.

V. Summary

The evidence shown in Section IV clearly demonstrates the efficacy of Prevnar in preventing acute otitis media due to pneumococci. The efficacy consists of significant reductions in both vaccine-serotype episodes and vaccine related serotype episodes, with marginal P-values less than 0.002 for both. There is some evidence, but considerably less clear (marginal P-values of 0.03, 0.060), to suggest an increase in AOM due to serotypes unrelated to vaccine serotypes. With all serotypes considered, the evidence supporting the efficacy of Prevnar is strong even when Bonferroni adjustment is used to account for multiple comparisons made within each category of the testing hierarchy.

The covariance analysis demonstrates that demographic and baseline variables such as gender, AOM history before 2 months of age, birth weight, gestational age, breastfeeding, daycare attendance, and household smoking do not change vaccine effect although they may have a strong effect on the AOM incidence in general. It is likely that the US population differs from the Finnish population with respect to the prevalence of these demographic risk factors for AOM, and as a result, may have a different AOM incidence from what was seen in the FinOM trial. However, the lack of significant interaction of these factors with vaccine effect suggests the efficacy results from Finland may be generalized to the United States population.

The estimate of vaccine effect against all cause AOM is similar for both the Finnish trial and the NCKP trial. However, the effect reached statistical significance in the NCKP trial but not in the Finnish trial. In light of the fact that the incidence of culture-confirmed pneumococcal AOM episodes in the Finnish trial was about 30% of the incidence of all cause AOM (0.36 and 1.24 episodes per child year respectively), it is not surprising to see the overall efficacy substantially lower than the efficacy against pneumococcal AOM, as the vaccine is not expected to prevent AOM due to other pathogens or AOM with no identifiable pathogens.

The vaccine effect seems to increase with the severity of AOM, showing increasingly larger point estimates from recurrent AOM to tube placement (Table A8). The observation is consistent with literature reports of pneumococcus being disproportionately responsible for more severe AOM episodes. The evidence of efficacy in recurrent AOM is strong in the NCKP trial but unclear in the Finnish trial due to the limitation of sample size.

The compilation of evidence of vaccine efficacy in tube placements is somewhat more complex. The reduction during PP follow-up in the NCKP trial reached a conventional significance level but not a Bonferroni adjusted level. With a larger number of events in the ITT follow-up, the

reduction was significant even with Bonferroni adjustment. A much smaller vaccine effect, however, was seen in the original FinOM efficacy trial. It was observed that the overall rate of tube placement during the trial was 3- to 4-fold higher than reported normal rates due to easier access to health care providers for subjects in the study possibly resulting in less severe cases having tube placements. The vaccine efficacy in the long-term follow-up of the original efficacy trial subjects until 4 to 5 years of age, a period when the subjects were under normal care rather than in a clinical trial setting, showed good evidence of vaccine effect. The reductions in the primary and secondary variables of the long-term follow-up both reached their respective significance levels. The extended follow-up in the NCKP further corroborates the efficacy in an older cohort. Considering the complete set of information (both trials and both the original and extended follow-up periods), a reduction in the rate of tube placements is supported.

Appendix 2: Additional Safety Information

1. **Labeling Changes (Completed and Proposed)**
2. **Overview of Safety Data from FinOM Study**

1. Labeling Changes Made or Proposed Regarding the Safety of Prevnar

As a result of routine postmarketing surveillance of spontaneous adverse event reports received by the company, the following adverse reactions have been added to the U.S. package insert since licensure of the product: injection site dermatitis; injection site urticaria; injection site pruritus; hypersensitivity reaction including face edema, dyspnea, bronchospasm; anaphylactic/anaphylactoid reaction including shock; angioneurotic edema; erythema multiforme. While these events have been reported very rarely, they are not unexpected for any vaccine in widespread usage and were felt to be of sufficient severity to warrant addition to the package insert. The safety of Prevnar continues to be monitored through postmarketing surveillance of adverse event reports, and additional changes to the U.S. package insert will be made as warranted.

In addition, we are currently proposing to CBER the following additions to the label in the Adverse Reactions Section:

Pre-Licensure Clinical Trial Experience

- a more detailed description of the occurrence of urticarial rashes from an additional analysis of the data from the NCKP efficacy study, that reads:

  In the large-scale efficacy study, urticaria-like rash was reported in 0.4%-1.4% of children within 48 hours following immunization with Prevnar administered concurrently with other routine childhood vaccines. Urticaria-like rash was reported in 1.3%-6% of children in the period from 3 to 14 days following immunization, and was most often reported following the fourth dose when it was administered concurrently with MMR vaccine. Based on limited data, it appears that children with urticaria-like rash after a dose of Prevnar may be more likely to report urticaria-like rash following a subsequent dose of Prevnar.

Postmarketing Experience

- lymphadenopathy localized to the region of the injection site,

- an Overdose sub-section that reads:

  There have been reports of overdose with Prevnar, including cases of administration of a higher than recommended dose and cases of subsequent doses administered closer than

recommended to the previous dose. Most individuals are asymptomatic. In general, adverse events reported with overdose have also been reported with recommended single doses of Prevnar.

2. An Overview of Safety Data in the FinOM Study (D118-P809)

1. Introduction

The number of subjects who were immunized with at least one dose of Prevnar in this study was small (N= 831), compared to that in the large-scale NCKP study (N=17,066) previously discussed at the VRBPAC meeting in November 1999. However, for completeness, an overview of the safety data collected in the FinOM study is presented in this document. Overall, there were no safety concerns based on this additional set of safety data, and the reactogenicity profile of the product appeared to be similar to that seen in other trials and reflected in the current product labeling.

2. Methodology

In this study, children were immunized at 2, 4, 6, and 12 months of age with either Prevnar or the control HBV. They were also immunized concurrently in the opposite limb with a DTP-Hib combination vaccine (either DTP-HbOC [Tetramune®] or DTP-PRP-T [Tetract-Hib®] at 2, 4, and 6 months of age and IPV (Imovax®) at 12 months of age. To determine acute reactogenicity, all children were observed after vaccination at the study clinics by the vaccinator for at least 15 minutes for any adverse reactions to vaccination. All parents were given a diary card after each vaccination for the recording of adverse reactions at 24, 48, and 72 hours after vaccination of their children. Specifically, parents were asked to check if the thigh was painful, red, or swollen at the site of each injection. They were further asked to measure the child's rectal temperature and to record if the children experienced excessive crying at 24, 48, and 72 hours following immunization. In addition, any other adverse events or serious adverse events reported during the entire study period through 24 months of age were recorded by study personnel.

3. Results

Prompted Local Reactions:

Injection site reactogenicity was statistically significantly more common for the DTP-Hib vaccine than for Prevnar at 24, 48 and 72 hours following doses 1, 2 and 3 for each local reaction. Relative frequencies of reactions at the Prevnar site vs. DTP-Hib site ranged across primary series doses as follows: tenderness or pain 3.4%-5.1% vs. 6.1%-8.9%, redness 14.2%-20.4% vs. 24.4%-35.5%, significant redness (>2.5cm) 0.0%-0.4% vs. 0.9%-1.5%, swelling 4.9%-5.7% vs. 14.5%-15.5% and significant swelling (>2.5cm) 0.5%-1.0% vs.

2.5%-5.8%. Concomitantly with the booster dose at twelve months of age, IPV was injected into the opposite thigh from Prevnar. Local reactions were more common in the Prevnar limb than in the IPV limb. The relative frequencies of reactions at the Prevnar site vs. IPV site were following: pain 7.6% vs. 5.0%, redness 15.5% vs. 10.2%, significant redness 0.8% vs. 0.1%, swelling 6.1% vs. 1.5% and significant swelling 1.3% vs. 0.0%. These differences were statistically significant.

When local reactions related to the study vaccine (Prevnar) were compared to the control vaccine (HBV), there were more reactions of all types and of any severity grade in the Prevnar group after each dose (pain 3.4-7.5% in the Prevnar group vs. 1.7-2.8% in HBV group, redness 14.2-20.3% in the Prevnar group vs. 9.5-15.9% in HBV group, swelling 4.9-6.2% in the Prevnar group vs. 1.8-5.8% in HBV group). Statistically significant differences were found only in pain after doses 2-4, in redness after doses 1 and 3, and in swelling after dose 1.

Prompted Systemic Reactions:

Fever (≥38.0°C) within 3 days following each vaccination was more common in the Prevnar group than in the HBV group. These differences were statistically significant after each dose. Fever rates in the Prevnar group were 14.7%, 19.3%, 25.5%, and 13.1% following doses 1 to 4, respectively, and were 9.6%, 13.2%, 13.8%, and 8.5% in the HBV group after each dose. DTP-Hib vaccine was administered concurrently with doses 1, 2, and 3, and IPV was administered concurrently with dose 4. The rates for moderate fever (>39.0°C) were less than or equal to 2% after each dose in each treatment group. More subjects in the Prevnar group experienced moderate fever after doses 1 to 3, but the difference was statistically significant only after dose 3.

Crying more than usual following immunization with Prevnar occurred statistically significantly more than in the HBV group following each dose (28.2% - 42.5% vs. 19.3%-36.8). Severe crying (continuously for more than 4 hours) occurred after 0 to 0.6% of Prevnar immunizations, and this was not significantly different from the HBV group (0 to 0.4%).

Other Adverse Events

For both Prevnar and HBV, there were no unusual frequencies in the incidence of serious adverse events of any type during the entire follow-up period. The overall rate of serious or unexpected adverse events tended to be smaller in the Prevnar group than in the HBV group.

One statistically significant difference between treatment groups in the primary diagnosis of SAE cases was detected: more suspected infections in the HBV group than the Prevnar group (13 vs. 4). The majority of these suspected infections were suspected bacteremias where the causative agent could not be identified (8 vs. 3).

Serious or Unexpected Adverse Events Considered Related to Immunization: There were 10 serious or unexpected events that were considered possibly related to immunization by the investigators. These were 5 urticarial rashes (3 in Prevnar, 2 in HBV), and one case of each of the following: hypotensive, hyporesponsive episode (HBV), rash (Prevnar), indefinite neurologic symptoms (excessive crying after Prevnar), transient granulocytopenia (Prevnar), and nonspecific inflammation of testicle (HBV). In all cases, DTP-Hib vaccine was administered concurrently with study vaccine, and all events occurred within 7 days of immunization.

Seizures:

Febrile: Fewer subjects in the Prevnar group experienced febrile seizures as compared to the HBV group. Within 3 days following immunization, there were no reports of febrile seizures in the Prevnar group and two in the HBV group. There were 2 subjects in the HBV group and 1 in the Prevnar group who experienced a febrile seizure within 14 days of immunization. Over the course of the entire study, a total of 14 subjects experienced 16 febrile seizure events in the HBV group and 11 subjects experienced 13 febrile seizure events in the Prevnar group.

Afebrile: No subjects in either vaccine group experienced an acute afebrile seizure within 3 days following immunization and no subjects in the Prevnar group experienced such an event within 14 days of immunization. Over the course of the entire study, 6 subjects in the Prevnar group and 1 subject in the HBV group experienced afebrile seizures: however, these did not occur in close temporal association with immunization, and it is not clear that these all represented true seizures. Neuroimaging studies, including EEG, revealed no abnormalities in any of these children, none of them received anticonvulsive medication, and they were all asymptomatic at the end of the follow-up.

Death: One child, enrolled in the Prevnar group, died during the study period. The death was due to a congenital anomalous mesentary leading to the obstruction and the necrosis of the bowel. Additional congenital anomalies were found in autopsy. The death occurred 85 days after dose 3, at the age of 8 months.

4. Safety Conclusion

In the FinOM Efficacy Study, Prevnar was significantly less reactogenic at the site of injection than the whole cell DTP-Hib vaccine, but more reactogenic than the Hepatitis b vaccine. For systemic events, Prevnar administered concurrently with either DTP-Hib or IPV resulted in a greater incidence of fever (≥38.0°C) within 3 days than did HBV administered with the same concurrent vaccines. However, the occurrence of a high fever (>39.0°C) was rare. The incidence of serious or unexpected adverse events considered related to immunization by the investigators was low in both the Prevnar and the HBV groups.

In conclusion, the safety of Prevnar was studied extensively prior to approval in the US, with the majority of safety data coming from the NCKP large-scale efficacy study. The safety profile of Prevnar seen in this much smaller FinOM study is similar to that which was seen in other pre-licensure trials and is currently reflected in the current product labeling. In addition, the safety of Prevnar is continuously being monitored by post-marketing studies as well as by the ongoing review of spontaneously-reported adverse events made to the company.

Appendix 3: Additional Information on the Analyses of PCR Data

In addition to the gold standard of culturing, the PCR assay was also used to detect pneumococcal organisms in all MEF samples. The results are summarized in Table A-1. Vaccine efficacy estimates for all pneumococcal episodes during PP follow-up were 34% based on culture-confirmed episodes and 20% based on culture- or PCR- confirmed episodes. When comparing the two methods of detection, there was only moderate concordance between them. A substantial number of samples were PCR positive for pneumococci but culture negative (532 and 486 samples in the Prevnar and HBV groups respectively). Other bacteria (*H. influenzae*, *M. catarrhalis*, *S. pyogenes*) were detected by culture in 42.6% of these samples. This is consistent with the previous finding in a Finnish study[32] in which other pathogens (*H.influenzae*, *M.catarrhalis*) were found in 23% of the PCR positive but culture negative MEF samples. When efficacy is calculated based on culture or PCR confirmed episodes, excluding episodes in which other bacteria were cultured, the efficacy is 30%. Although PCR has been found to be specific for pneumococci, the clinical significance of a positive PCR in MEF that is culture negative for *S. pneumoniae* but culture positive for other known otitis media pathogens is unknown. While PCR could represent a more sensitive probe for actual pneumococcal otitis media, it may also be detecting pneumococcal organisms present in small numbers but not contributing to the pathogenesis of the acute event. Based on this, it seems prudent to continue to consider culture as the "gold standard" for detection of *S. pneumoniae* in a given specimen.

Table A-1: Efficacy Results of All Pneumococcal AOM Episodes Using PCR and Culture

Follow-up Period	Method of Diagnosis	Number of Episodes		Rate/person year		Vaccine Efficacy (%)	
		HBV	Prevnar	HBV	Prevnar	Estimate	95% CI
PP							
	Determined by culture	414	271	0.36	0.23	34	(21, 45)
	Determined by PCR	678	541	0.60	0.48	20	(7, 31)
	Determined by culture or PCR	687	548	0.60	0.48	20	(7, 31)
	Determined by PCR / excluding Culture Confirmed *H. flu, M.cat, and S. pyo*	459	321	0.40	0.28	30	(17, 41)
	Determined by PCR or Culture / excluding Culture Confirmed *H. flu, M.cat, and S. pyo*	466	325	0.40	0.28	30	(17, 41)
ITT							
	Determined by culture	467	322	0.32	0.22	32	(19, 42)
	Determined by PCR	764	635	0.54	0.44	18	(5, 29)
	Determined by culture or PCR	775	642	0.54	0.45	18	(5, 29)
	Determined by PCR / excluding Culture Confirmed *H. flu, M.cat, and S. pyo*	527	396	0.37	0.27	25	(13, 36)
	Determined by PCR or Culture / excluding Culture Confirmed *H. flu, M.cat, and S.pyo*	536	400	0.37	0.28	26	(13, 37)

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